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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,198	03/10/2004	Michael J. Munchhof	PC23318A	6197

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PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
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GROTON, CT 06340

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 04/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/798,198	MUNCHHOF, MICHAEL J.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *5-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

A Requirement for Restriction was mailed on 6 February 2006. In applicant's reply to that Requirement, filed 6 March 2006, the invention set forth as Group I was elected (claims 1-11), and the species of Example 3 from the specification was further elected as a single disclosed species from which a search of the relevant prior art will begin.

Although the reply to the Requirement for Restriction indicates that the election is made with traverse, applicant's counsel has not distinctly and specifically pointed out the supposed errors in the restriction requirement.

Based on the structure of the elected species for examination, which is the compound of newly added claim 19, "3-amino-6-phenyl-pyrazine-2-carboxylic acid benzyl amide," a search of the prior art was begun, said search being focused on those compounds according to instant claim 1 wherein R^1 is H (in other words, those compounds according to claim 1 with R^1 and R^2 *not* being joined to form a ring together with the nitrogen atom to which they are both attached). Prior art anticipating claims 1-4 was found, whereupon the search of Group I claims was stopped. Claims 5-11 are therefore withdrawn as not being readable on the elected species, pursuant to "Markush practice" explained in MPEP 803.02.

Claims 1-4 have not been completely searched; the embodiment of those claims wherein R^1 and R^2 are joined to form a substituted or unsubstituted "heterocycloalkyl" or heteroaryl has not been searched.

Claims 12-14 are also withdrawn, as not being drawn to the elected invention.

In total, claims 5-14 are withdrawn from consideration at this time.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 15-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of formula (I), pharmaceutically acceptable salts and hydrates thereof, does not reasonably provide enablement for prodrugs and solvates of the compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In making the determination of whether or not a claimed invention is supported by a given disclosure to sufficient to enable a person of ordinary skill in the art to which it pertains, to make and/or use the invention, given said disclosure, the Office relies upon factors promulgated in the decision rendered in *In re Wands*:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, 858 F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

Each factor will be addressed, first with respect to the non-enabled solvates, and then with respect to the non-enabled prodrugs.

- *Solvates are not enabled*:

(A) Insofar as the solvate embodiment of claims 1-4 and 15-19 is concerned, those claims read on solvates of compounds according to formula (I). The scope of these solvates recited in the claims includes solvates of a compound according to formula (I), with *any* solvent. The definition of a solvate, taken from the Vippagunta et al reference, cited in section (C), (D), (E) below, is a "crystalline solid adduct[s] containing solvent molecules within the crystal structure, in either stoichiometric or nonstoichiometric proportions, giving rise to unique differences in the physical and pharmaceutical properties of the drug." The number of specific solvates, embraced by instant claim 1, and the claims that depend from that claim, is essentially incalculable.

(B) The nature of the invention is that of a chemical compound's specific solvate forms.

(C), (D), (E) Solvates, at the time the invention was made, were known and could be identified, but not understood to such an extent that the directed preparation thereof was routine or simple. The following references address the state of the art with respect to crystalline forms of organic compounds, formation of solvates of organic compounds, and the predictability thereof.

Vippagunta et al, "Crystalline Solids" Advanced Drug Delivery Reviews, vol. 48, pages 3-26 (2001).

and

Gavezzotti, "Are Crystal Structures Predictable?" Accounts of Chemical Research, vol. 27, pages 309-314 (1994).

First, it is evident from both of the references that formation of specific crystalline forms, and more particularly, solvates, is highly unpredictable. See Gavezzotti, page 312, point #8, and Vippagunta et al, page 11, "Prediction of Polymorphs" and page 18 "Prediction of the formation of hydrates and solvates."

Because the formation of solvates is unpredictable, even the relatively high level of skill possessed by one of ordinary skill in the art is not enough to render preparation of solvates routine. Each solvate of each compound must be experimentally prepared (since the conditions necessary for the formation cannot be predicted), wherein all of the factors relevant to each individual compound's ability to crystallize and form solvates are studied. These factors are identified in points #1-7 of the Gavezzotti reference. The preparation of each single claimed solvate represents a significant undertaking in the areas of preparative organic chemistry, physical chemistry, and crystallographic measurements.

It is unknown that the full scope of solvates of compounds of formula (I) is even possible (see Gavezzotti, page 309, point #1).

(F) Aside from a mention that the invention includes solvates of formula (I) compounds (at page 1, line 18) no guidance relevant to preparation of solvates is provided in the disclosure.

(G) No working examples, out of the over two hundred provided, demonstrate preparation of a solvate. The specification states that the procedure employed for Example 1 was followed for the preparation of the compounds described in the Tables. Example 1 teaches isolation of the compound of the invention in crude form from *N*,*N*-dimethylacetamide and then purified from ethyl acetate, but even then, no solvate of any compound of formula (I) with *N*,*N*-dimethylacetamide or ethyl acetate is identified.

(H) Each compound of formula (I), of which there are thousands upon thousands, as a solvate with every solvent within the scope of "solvate" generally, of which there are also thousands upon thousands, represents the efforts of many over a period of years. Those efforts are likely never to be completed, due to the sheer number of possible

compound/solvent combinations. For one of ordinary skill in the art to conduct the type of research outlined in Gavezzotti and in Vippagunta et al for preparation of every one of the claimed solvates would clearly be undue. Applicants' right to exclude others from making all solvates of compounds according to formula (I) is unwarranted in light of the lack of any direction as to how one of ordinary skill would do so.

Since, as taught in Vippagunta et al (column one of page 15), hydrates are a special type of solvate, due to the small size and extremely polar nature of the water molecule, preparation of hydrates of formula (I) is deemed to be within the purview of a chemist of ordinary skill. It would not be undue for a chemist to determine which compounds according to formula (I) will not form hydrates and which of them will, and how to make and identify those hydrates. "Solvates" generally, however, represents a hugely more involved task.

- *Prodrugs are not enabled*:

(A) Though it might appear that the prodrugs embodiment of instant claim 1, from which claims 2-4 and 15-19 depend, is limited only to compounds of formula (I) having the structure depicted, it is not. A prodrug, as defined by Bundgaard in:

Hans Bundgaard, Design of Prodrugs, page 1. © 1985 Elsevier Science Publishers.

"is an inactive species, and therefore, once its job is completed, intact prodrug represents unavailable drug." Thus, an important requirement of prodrugs of compounds of formula (I) is that they be pharmacologically inactive (this is in fact noted at page 14, line 27 of the instant specification). Prodrugs come in myriad forms, and are not limited to only those which undergo some sort of enzymatic solvolysis, which are commonly cited as examples, and suggested as the preferred type of prodrug in the paragraph bridging pages 14 and 15 of the instant specification, like esters or other

acylated derivative. A prodrug may be a Mannich base (imine), an acyclic precursor to a heterocyclic compound, a polymer-bound drug (either covalently or ionically), a compound of the drug covalently or ionically bound to another drug with different action or a carboxylic acid which is decarboxylated to provide the active drug.

So, the scope of all prodrugs is quite broad. A prodrug does not necessarily depend on the identity of the pharmacologically active agent formed from the prodrug for patentability. A prodrug is not necessarily even structurally related to the compound of which it functions as a prodrug, since the metabolism *in vivo* of that compound is what provides the drug.

(B) Prodrugs of a compound of formula (I) are the nature of the invention.

(C) The state of the prior art with respect to the development of prodrugs is represented by:

> Richard B. Silverman, The Organic Chemistry of Drug Design and Drug Action, pages 352-400. © 1992 Academic Press, Inc.

Silverman, cited in the specification at page 15, teaches many kinds of prodrugs, including all of the types mentioned above in section "(A)." Pages 353 and 354 list eight various reasons why a prodrug is desirable. On page 354, Silverman teaches that some prodrugs are discovered accidentally, and some designed on the basis of known metabolic transformations.

(D) The level of ordinary skill in the art insofar as the prodrug embodiment of instant claims 1-4 and 15-19 is concerned is that of a medicinal chemist, holding a graduate level degree in the field and with experience in preparative organic chemistry.

(E) As discovery of prodrugs is sometimes accidental, then it follows that whether a given compound will function as a prodrug or not is sometimes unpredictable. On the

other hand, when a compound is designed as a prodrug, one must first understand the metabolic milieu into which the presumptive prodrug is to be introduced, and must also know to what extent the compound will be metabolized. The metabolism of xenobiotics is not always predictable. A prodrug must also, by definition, be pharmacologically inactive, so one must know which modifications of the structure of the parent compound will render it inactive. Structure-activity relationships must in large part be determined empirically, although once a rule is discerned, the structure-activity of a given series of compounds becomes predictable.

Theoretically, if one of ordinary skill in the art knew all of the above variables, prodrug structure could be predicted in advance. The reality is that all of these considerations, in total, must be empirically derived when the compound in question is an *[*allegedly*]* novel compound, as are compounds of formula (I). It cannot be predicted which compounds will serve as prodrugs for formula (I) compounds.

(F) No specific guidance relevant to the preparation of prodrugs of formula (I) compounds is provided in the specification.

No metabolic studies of the compounds *in vivo* have been done and no structure-activity rules are outlined – certainly no teaching as to which modifications will afford an *inactive* compound is found in the specification. The specification does not specifically address any type of prodrug other than acylated derivatives.

(G) No working examples, out of the seven preparative examples, of a prodrug are in the disclosure.

(H) In order for one of ordinary skill in the art to practice the full scope of the prodrugs of compounds of formula (I), a complete structure activity analysis of all of the compounds falling within formula (I) would have to be completed. This analysis would

involve thousands upon thousands of individual compounds. The practitioner would first screen for which type of modifications of the molecular structure would render an inactive compound. Then, the metabolic studies of all of these inactive compounds would have to be completed, and compounds that are converted to active compounds of formula (I) *in vivo* identified. This research would potentially be inconclusive and could take years. A major part of the work necessary for realizing the full scope of prodrugs of formula (I) compounds would be that pertaining to totally new compounds not bearing any structural similarity to the compounds of formula (I), such as the procyclic compounds converted to heterocyclic compounds *in vivo*, which are mentioned on page 360 of Silverman. Work with polymeric forms of the compounds of formula (I) would be necessary also. Because different animals' metabolisms differ to the extent that xenobiotics (drugs, in other words) are handled by different enzymatic pathways, this effort would have to be duplicated in each species for which a certain prodrug of a formula (I) compound were sought. As evidence that animals will differ substantially in the manner that xenobiotics are metabolized, the examiner presents:

> Al-Dabbagh and Smith, "Species differences in oxidative drug metabolism: some basic considerations." Archives of toxicology. Supplement. Archiv fur Toxikologie. supplement, vol. 7, pages 219-231 (1984).

Al-Dabbagh and Smith states that the metabolic process itself is highly variable both between and within animal species, and that the toxic effect of many chemicals is a function of how the chemical is metabolized rather than the substance itself.

Given the amount of direction in the disclosure, this amount of experimentation is clearly undue. Applicants have not described the manner and process of making prodrugs of compounds of formula (I), in such full, clear, concise, and exact terms as to enable any person skilled in the art to do so.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 and 15-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "prodrug" renders the scope of instant claim 1, and therefore any claim which depends therefrom, indefinite in scope.

Applicants may opine that one of ordinary skill understands what the term "prodrug" means. The examiner is not pretending that one of ordinary skill does not understand what *function* a prodrug serves. This is not the issue here. What is claimed is chemical compounds which serve as a prodrug for the compounds of formula (I). The claim, therefore, is drawn to a group of *molecular structures*, that when subjected to a biological milieu in a live animal, will be metabolically converted to a compound of formula (I). One of ordinary skill cannot possibly be aware of the full scope of all of the different molecular arrangements which will provide the compounds (I) upon being metabolized, in all animals. Page 14 of the specification only provides a few examples of what applicants intend the term to encompass. The only type of prodrug discussed is ester derivatives.

As evidenced by the Al-Dabbagh and Smith reference, cited *supra*, in the rejection of the claimed prodrugs under the first paragraph of 35 U.S.C. 112, animals will differ significantly in the manner that xenobiotics are metabolized. Therefore, a

compound that is a prodrug in humans is not necessarily a prodrug in a cat, for example. So, which compounds will act as prodrugs for a certain formula (I) compound will not necessarily be the same in different animal species. Arguably, therefore, the identity of the prodrugs according to instant claim 1 will differ based on the animal to which the prodrug is to be administered. Since no animal species is recited in instant claim 1, with respect to the prodrugs, the identity of the prodrugs is dependent on an undefined variable.

Claim 1 is further indefinite because the terms "amide" and "heterocycloalkyl," in the definition of R^2, and "sulfonyl" and "keto," in the definition of R^3, are not clear and well-defined in the specification.

"Amide" is normally thought of as an organic acid group which has had an –OH moiety replaced with a nitrogen atom – such as a carboxamide R-C(O)NH_2, a sulfonamide R-S$(O)_2NH_2$ or a phosphonamide R-P(O)(OH)NH_2. So, a structural variable which is bonded to an carboxamide nitrogen atom, when defined as an "amide" is somewhat redundant. It is not understood whether the "amide" identity for R^2 is some functional group bonded to the nitrogen atom which converts that nitrogen atom to an amide, like an acyl group –C(O)-R or if that is not the case, whether the amide (be it a carboxamide, sulfonamide, phosphonamide) is bonded *via* the acidic part or *via* the nitrogen atom. No definition is provided for the term in the instant specification.

"Heterocycloalkyl" is not understood. The term could be referring to a heterocyclic group bonded *via* an alkyl group, or to a cycloalkyl group comprising a heteroatom. No definition is provided for the term in the specification, although the related terms "heterocyclic," "heterocycle," "heterocyclyl" and "heteroaryl" are

satisfactorily defined in the specification. The term "heterocycloalkyl" is not synonymous with either of "heterocyclic," "heterocycle," "heterocyclyl" or "heteroaryl."

"Sulfonyl" generally refers to and is understood by chemists of ordinary skill to signify a radical composed of sulfur atom double bonded to two oxygen atoms – $RS(O)_2$-. Since no other qualifier is recited in connection with "sulfonyl" the term is not complete. The orientation of the sulfonyl group is not known from the recitation of "sulfonyl," in other words, the group could be bonded through the sulfur atom or through some linking group like an alkylene group, or any other heteroatom for that matter. The term "sulfonyl" when recited as a substituent group by itself amounts to an incomplete definition for a structural variable. There is no definition for the term "sulfonyl" provided in the instant specification.

"Keto," similar to "sulfonyl," is not a complete definition for an identity of a monovalent structural variable in a molecular structure diagram. A "keto" group, with no other modifying language, would be a divalent carbonyl group, –C(O)–. Since R^3 in formula (I) is a monovalent substituent, a "keto" identity for R^3 is not a possible bonding arrangement. No definition of "keto" is provided in the instant specification.

Claim 2 is further indefinite, in addition to being indefinite because it depends from indefinite base claim, is indefinite because the base claim, claim 1, does not provide antecedent basis for the $(C_1$-$C_8)$alkyl-SO_2- or $(C_1$-$C_8)$alkylC(=O)- recited as identities for R^3 therein. The "sulfonyl" and "keto" groups set forth as alternatives for R^3 in claim 1 do not include alkylsulfonyl and alkylcarbonyl (which would properly be denoted "acyl"). "Sulfonyl" by itself and "keto" by itself are just that, a sulfonyl group and a keto group. Claim 2 adds something to an element of claim 1 which is not permitted.

Claims 3, 4 and 15-19 are included in this rejection, although no specific defects of those claims under the second paragraph of 35 U.S.C. 112 have been pointed out, because those claims depend from and therefore incorporate the limitations of indefinite claim one.

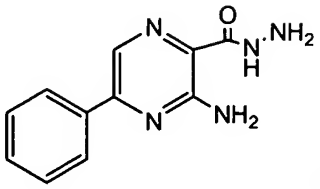
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by WO 02/48152 (Bakthavatchalam et al), which is cited in the Information Disclosure Statement filed by applicant 18 June 2004 and published 20 June 2002, less than one year before the instant invention was made. The filing date of the international application, 11 December 2001, is a proper date under 102(e) because the reference was published in the English language and designates the United States.

A compound according to claims 1-4 is employed as an intermediate in the preparation of Bakthavatchalam et al's NPY5 receptor ligands. On page 54, in Example 8, the compound, misnamed as "2-amino-5-phenyl-nicotinic acid hydrazide," and having the following structural formula (appears on the next page):



is employed in the synthesis of a imidazo[4,5-b]pyrazine ring containing compound, so clearly if the target compound is a pyrazine ring-containing compound, then the nicotinic acid compound named is incorrect (nicotinic acid would be the corresponding pyridine-ring containing compound instead of pyrazine). The correct name of the compound shown by its structural formula is 3-amino-5-phenyl-pyrazine-2-carboxylic acid hydrazide.

This compound is a compound according to instant claims 1-4 wherein R^2 is amino and n=0 and R^3 is H, $(C_1\text{-}C_8)$alkyl, halo, $(C_1\text{-}C_8)$alkoxy or cyano.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by De Meester et al, "Synthesis of 3-Alkyl-6-Phenyl-4(3*H*)-pteridinones and their 8-Oxides. Potential Substrates of Xanthine Oxidase" *Journal of Heterocyclic Chemistry*, vol. 24, pages 1109-1116 (July-August 1987).

On page 1110, De Meester et al report the synthesis of these pteridinone compounds, via a phenylpyrazine carboxamide intermediate. The various intermediates employed are shown by structure diagram **4 a-h**. Of these compounds, **4d**, **4f**, **4g**, **4h** are excluded by the proviso at the end of instant claim 1. Three of the compounds are the various permutations of butyl-substituted amide (*n*-butyl, *sec*-butyl, *tert*-butyl) and one is the hydroxymethyl-substituted amide.

Five of the compounds are embraced by instant claim 1, however, these are **4a**, **4b**, **4c**, **4e**, **4i** and **4j**, which are compounds according to instant claims 1-4 wherein R^2 is methyl, ethyl, *n*-propyl, isopropyl, and two isomers of hydroxy-*sec*-butyl, with of

formula (I) being equal to zero, and R^3 being selected from H, (C_1-C_8)alkyl, halo, (C_1-C_8)alkoxy or cyano.

Allowable Subject Matter

Claims 15-19 would be allowable if rewritten to overcome the rejections under 35 U.S.C. 112, first and second paragraphs, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

The closest prior art with respect to compounds according to claims 15-19 is the Bakthavatchalam et al and DeMeester et al references cited herein. Neither of the two references suggest a compound according to formula (I) where R^2 is an alkylaryl group, specifically $-CH_2-$phenyl (benzyl).

Upon amendment of the application to overcome the rejections set forth herein, placing the claims of the elected Restriction Group in condition for allowance, the claims of the nonelected Group, claims 12-14 will be rejoined and the Requirement for Restriction between Groups I and II withdrawn. At such time, a rejection of claims 13 and 14 under the first and second paragraphs of 35 U.S.C. 112 will be necessary, on grounds that a. the scope of the phrase "TGF-related disease state" is not known or understood by those of ordinary skill in the art of medicine (physicians, that is) and b. neither preventing nor treating any disease with a compound of formula (I) is enabled by the disclosure, specifically and especially because no biological data whatsoever is presented in the specification. Whether compounds of formula (I) have any pharmacological effect at all is unknown. Even in the presence of some *in vitro* data showing formula (I) compounds have some activity inhibiting the TGF-β signaling pathway, one of ordinary skill would be at a loss on how to practice the full scope of instant claims 13 and 14, specifically how to treat or prevent any and all cancers, with a

compound according to the invention. It is therefore suggested, to avoid further delay in allowance and issue of this application, that applicant cancel claims 13 and 14 in response to this Office action.

Abstract of the Disclosure

In the Requirement for Restriction letter mailed prior to this Office action, objection to the abstract of the disclosure of the instant application was voiced, on grounds that the abstract, which merely states that the compounds of the invention are pyrazine compounds, is no more descriptive than the title of the application. Applicant's counsel has not addressed this objection, therefore, it is maintained.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Tuesday-Thursday from 8:00am to 4:30pm or Monday from 6:00am to 1:30pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

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